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# Does infection with or vaccination against SARS-CoV-2 lead to lasting immunity?



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Many nations are pursuing the rollout of SARS-CoV-2 vaccines as an exit strategy from unprecedented COVID-19-related restrictions. However, the success of this strategy relies critically on the duration of protective immunity resulting from both natural infection and vaccination. SARS-CoV-2 infection elicits an adaptive immune response against a large breadth of viral epitopes, although the duration of the response varies with age and disease severity. Current evidence from case studies and large observational studies suggests that, consistent with research on other common respiratory viruses, a protective immunological response lasts for approximately 5–12 months from primary infection, with reinfection being more likely given an insufficiently robust primary humoral response. Markers of humoral and cell-mediated immune memory can persist over many months, and might help to mitigate against severe disease upon reinfection. Emerging data, including evidence of breakthrough infections, suggest that vaccine effectiveness might be reduced significantly against emerging variants of concern, and hence secondary vaccines will need to be developed to maintain population-level protective immunity. Nonetheless, other interventions will also be required, with further outbreaks likely to occur due to antigenic drift, selective pressures for novel variants, and global population mobility.

## Introduction

Since its emergence in December 2019, SARS-CoV-2 has continued to cause a considerable burden of acute and chronic disease, placing immense pressure on health systems worldwide. To break chains of transmission and slow the surge in morbidity and mortality associated with the pandemic, governments have employed a range of non-pharmaceutical interventions, including social distancing, mask wearing, testing, contact tracing, travel restrictions, and quarantining. However, the cost of these measures has been a social and economic toll unparalleled in scope.<sup>1</sup>

Improvements in testing capacity, alongside news of the efficacy of novel vaccines<sup>2–4</sup> and their rollout for many populations worldwide, provide much hope compared with the worrying public health outlook of 2020. Nonetheless, emerging data on novel genetic variants of SARS-CoV-2,<sup>5</sup> together with evidence of potential reinfections,<sup>6–19</sup> threaten the notion of immune protection following a primary infection and—of equal, if not more, concern—after vaccination. If the durability of immunity is hindered by changes in the genetic architecture of circulating SARS-CoV-2 strains, this would have key implications for relaxing the stringency of non-pharmaceutical interventions.

To understand the extent of this potential threat, in this Personal View we evaluate research on common respiratory viruses and previous pandemic human coronaviruses, and draw on the large body of emerging immunological data on SARS-CoV-2 infection. We focus on the developing knowledge of cellular and humoral immunity to SARS-CoV-2, in response to both natural infection and vaccination, and present our views on what the available evidence means in terms of the longevity of protective immunity. We discuss areas of concern regarding the emergence of novel variants of SARS-CoV-2 and the growing evidence of human reinfection, and

## Key messages

- The duration and breadth of the humoral response to SARS-CoV-2 infection varies markedly by age and disease severity, with detectable neutralising responses present for up to 1 year after infection; memory B cells raised against the viral spike protein and its receptor binding domain are maintained in frequency for many months after recovery from infection and are able to generate potent neutralising antibodies upon viral rechallenge
- Evidence from animal models, patient case studies, and large observational studies suggests that the time to reinfection is approximately 5–12 months, with individuals who were initially seropositive for IgG antibodies having a lower risk of reinfection
- The cell-mediated response seems to be more polyeptopic than that of the humoral system, and the magnitude of the response greater in younger patients with less severe disease; a potent spike-specific memory T-cell response persists for 5–8 months after infection and might be mounted even in the presence of low neutralising antibody titres, reducing disease severity upon rechallenge
- Vaccination elicits a spike-specific immune response of greater specificity and magnitude than that of natural infection, but emerging data suggest that protective immune responses, predominantly viral neutralisation, and vaccine effectiveness against infection are impaired against variants of concern
- Given the considerable viral epitopic mutation, it is likely that SARS-CoV-2 vaccines will need to be updated on a seasonal or yearly basis to maintain population-level protective immunity, as is the case with other endemic respiratory viruses; other interventions might also be required to prevent the occurrence of further significant outbreaks and reduce the incidence of disease

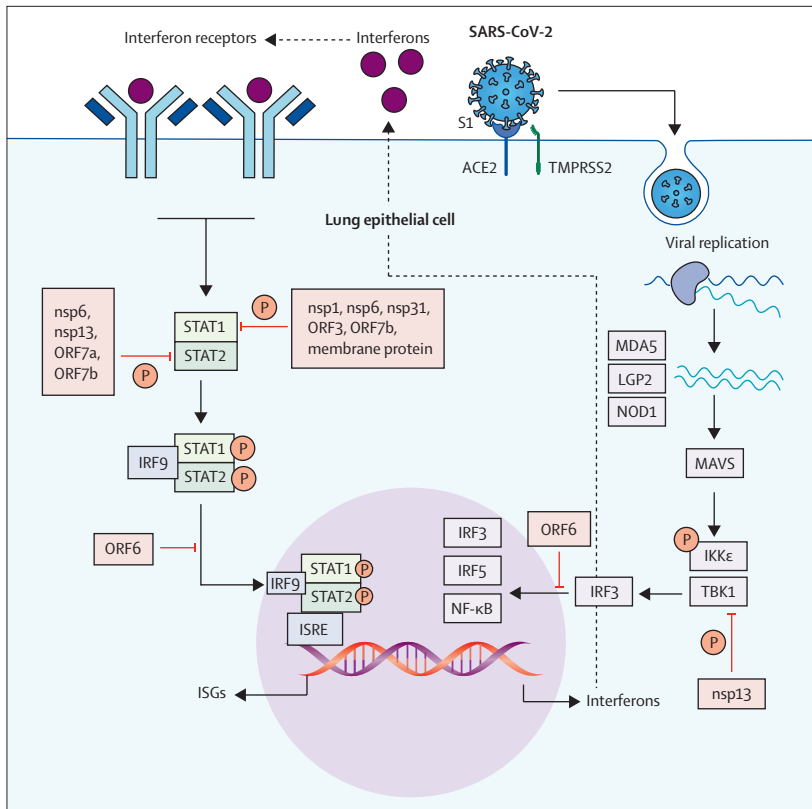
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**Figure 1: Molecular mechanisms of innate immune activation after SARS-CoV-2 infection**

SARS-CoV-2 enters host cells via interactions between the surface unit S1 of the S protein and host ACE2 and TMPRSS2, followed by endocytosis and viral genome release into the cytosol.<sup>22</sup> Intermediate double-stranded RNA forms, present during viral replication, are recognised as PAMPs by various cytosolic host PRRs, including MDA5, LGP2, and NOD1.<sup>23</sup> These PRRs signal through MAVS to activate a plethora of downstream components, in turn causing activation of IKKε and TBK1. These kinases phosphorylate IRF3, which dimerises and translocates to the nucleus where it activates various transcription factors (NF-κB, IRF3, IRF5) to induce transcription of genes encoding type I interferons.<sup>24–26</sup> The host cell also has type I interferon receptors with extracellular domains that bind type I interferons, leading to a molecular cascade via the JAK–STAT pathway that culminates in the binding of the STAT1–STAT2–IRF9 heterodimer to the ISRE and the stimulation of ISGs, which exert various antiviral effects.<sup>23</sup> SARS-CoV-2 can evade the antiviral effects of type I interferons by various molecular mechanisms. For example, nsp13 blocks phosphorylation of TBK1 and hence activation of IRF3, and various nsps and ORFs prevent phosphorylation of STAT1 and STAT2, in turn preventing the formation of the interferon-stimulated gene factor (ie, the STAT1–STAT2 heterodimer bound to IRF9). ORF6 also binds importin and blocks nuclear translocation of both STAT1 and IRF3, downregulating expression of ISGs and production of interferons.<sup>24</sup> ACE2=angiotensin-converting enzyme 2. IKKε=inhibitor of κ-B kinase ε. IRF=interferon regulatory factor. ISGs=interferon-stimulated genes. ISRE=interferon-stimulated regulatory element. JAK=Janus kinase. LGP2=laboratory of genetics and physiology 2. MAVS=mitochondrial antiviral-signalling protein. MDA5=melanoma differentiation-associated protein 5. NF-κB=nuclear factor kappa-light-chain-enhancer of activated B cells. NOD1=nucleotide-binding oligomerisation domain containing 1. nsp=non-structural protein. ORF=open reading frame. P=phosphorylation. PAMPs=pathogen-associated molecular patterns. PRRs=pattern recognition receptors. S=spike. STAT=signal transducer and activator of transcription. TBK1=TANK-binding kinase 1. TMPRSS2=transmembrane protease serine 2.

identify priorities for research to address current gaps in understanding.

### SARS-CoV-2 immunity in context

SARS-CoV-2 belongs to the *Coronavirinae* subfamily of positive-sense RNA viruses, which includes four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. Within the *Coronavirinae* are viruses that are frequently responsible for mild upper respiratory tract infections in humans: HCoV-229E,

HCoV-NL63 (alphacoronaviruses), HCoV-OC43, and HCoV-HKU1 (betacoronaviruses).<sup>20</sup> Other betacoronaviruses include the previous pandemic viruses SARS-CoV and MERS-CoV, which spilled over into human populations from bats and dromedary camels.<sup>21</sup> Although there are differences in the epidemiology of these various human coronaviruses, relevant insights can be gleaned on the host immune response to infection. For instance, SARS-CoV-2 has evolved various mechanisms to evade the innate immune response to infection (figure 1), with host recognition mechanisms and viral immune evasion pathways showing some similarities to those of previous pandemic coronaviruses.<sup>22–26</sup>

Studies following patients who have recovered from SARS-CoV have found that circulating IgG responses are detectable for 2–3 years after infection,<sup>27,28</sup> and neutralising antibodies have been identified after more than 6 months<sup>29,30</sup> and even up to 12 years after infection.<sup>31</sup> Similarly, in patients who have recovered from MERS-CoV, neutralising antibodies have been detected up to 18 months after infection.<sup>32</sup> Albeit in a small cohort, a correlation was also found between disease severity and antibody longevity: asymptomatic patients were seronegative, whereas those recovering from severe disease had detectable antibodies 34 months after infection.<sup>33</sup> Animal models of MERS-CoV have shown that an inability to generate neutralising antibodies results in enhanced inflammation and poorer clinical outcomes upon viral rechallenge, suggesting an important role for neutralising antibodies in preventing reinfection by coronaviruses.<sup>34</sup>

Among other respiratory viruses, including the seasonal coronaviruses, respiratory syncytial virus, and influenza virus, infection tends to lead to the production of neutralising antibodies that are transiently protective against reinfection.<sup>35</sup> Natural infection studies have shown that waning protective immunity allows for reinfection with seasonal coronaviruses within a 12-month window (although strain variation, not accounted for in these studies, might partly explain this short-lived immunity).<sup>36,37</sup> In a study of adults naturally infected with respiratory syncytial virus, 73% (11 of 15) were reinfected within an 8-month period,<sup>38</sup> whereas in an infant study, 36% (45 of 125) were reinfected in a 24-month period from birth, with the risk of reinfection negatively correlating with the neutralising antibody titre from the previous infection.<sup>39</sup>

### Humoral immunity in natural SARS-CoV-2 infection

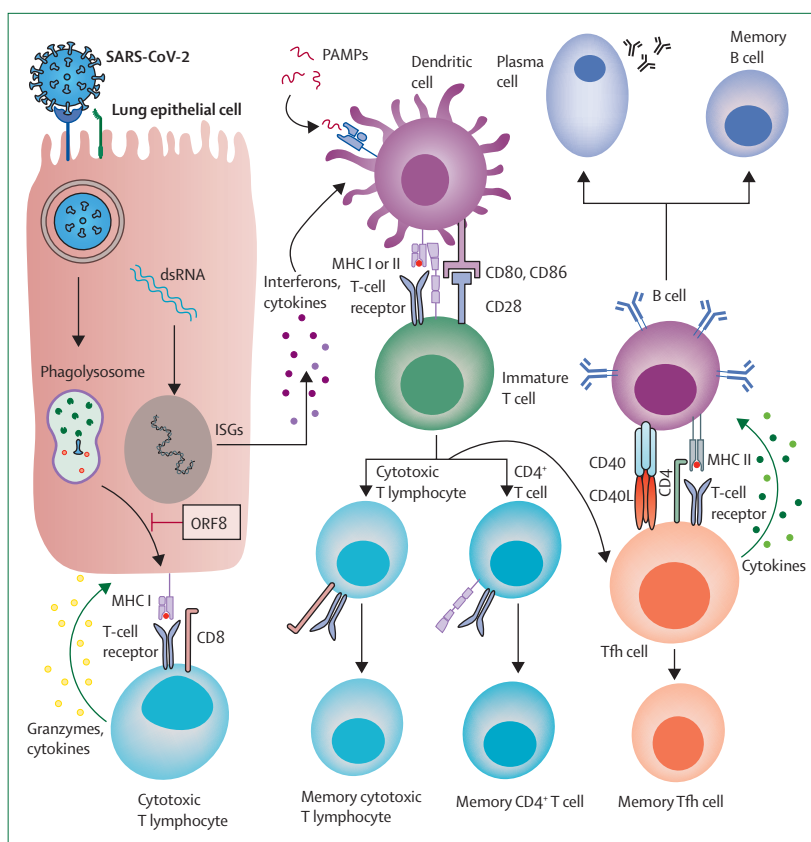
The presence of neutralising antibodies is typically seen as one of the best correlates of effective immunity for a variety of pathogens.<sup>40</sup> Nonetheless, key challenges to understanding long-term immunity to SARS-CoV-2 are the lack of consensus on immune correlates of protection and the current paucity of human rechallenge studies. The first human challenge study, including 90 participants aged

18–30 years, began in February 2021 at Imperial College London, UK,<sup>41</sup> and although data are not yet available, the first three volunteers completed quarantine with no unexpected issues.<sup>42</sup> Studies examining the immune response in animals have shown that SARS-CoV-2 infection elicits a robust humoral response,<sup>43–45</sup> probably contributing to protection against reinfection for up to 28 days in ferrets<sup>46</sup> and 35 days in Rhesus macaques.<sup>47</sup> In humans, various studies have shown that almost all convalescent patients mount detectable neutralising antibody responses,<sup>48–50</sup> and that, similar to other respiratory virus infections,<sup>35–37,39</sup> a humoral response substantially reduces the risk of reinfection.<sup>6–19</sup>

### Moderate-to-severe disease

In critical cases of COVID-19, in which individuals require mechanical ventilation for several weeks as a result of acute respiratory distress syndrome, antibodies are raised against a range of viral antigens, with the majority of neutralising antibodies targeting epitopes on the spike protein (the viral envelope protein that mediates entry into host cells) and its receptor binding domain (RBD; the part of the spike protein required for viral binding to the host angiotensin-converting enzyme 2 [ACE2] receptor; figure 1).<sup>22,51–55</sup> Although there is substantial heterogeneity between individuals in the duration of antibody responses,<sup>50</sup> patients with more severe disease, compared with milder disease, tend to have higher initial neutralising antibodies titres,<sup>56–58</sup> but emerging evidence suggests that these differences are lost within a few months owing to rapidly waning titres.<sup>57</sup> These antibody dynamics are consistent with those of other acute infections, including seasonal and pandemic coronaviruses,<sup>33</sup> and probably result from transient increases in plasmablast populations following infection (a short-lived stage between post-germinal centre B cells and plasma cells; figure 2).<sup>57,59–62</sup>

Although accurate measures of antibody duration are hampered by inconsistencies among immunoassays<sup>63</sup> and the short length of many published longitudinal studies, several studies undertaken over longer time periods are now available, providing key insights into long-term antibody dynamics. For instance, one study found anti-spike and anti-RBD IgG and neutralising activity to persist in the majority of patients (90% and 60%, respectively) 9–11 months after symptom onset.<sup>64</sup> Another study showed that neutralising antibody responses were mounted 2 weeks after symptom onset in 101 of 150 (67·3%) patients (mostly admitted to hospital), and persisted for more than 8 months after symptom onset in all but three patients.<sup>65</sup> Overall, these and other data<sup>66,67</sup> are consistent with detectable neutralising antibody responses lasting 8–12 months in patients with severe disease. Although this represents the current best estimate, as the time since SARS-CoV-2 emergence increases, longer follow-up periods will become feasible, further increasing the accuracy of such



**Figure 2: Overview of the adaptive immune response to SARS-CoV-2**

The detection of viral RNA in infected epithelial cells leads to the production of interferons and proinflammatory cytokines. Dendritic cells recognise the presence of PAMPs (eg, viral RNA) and inflammatory markers (eg, interferons), leading to their activation. Activated dendritic cells migrate to lymph nodes and present antigen (on MHC class I or class II molecules) and co-stimulatory molecules to immature T cells, which differentiate into CD8<sup>+</sup> cytotoxic T lymphocytes, CD4<sup>+</sup> T cells, or Tfh cells (all of which can differentiate into long-term memory cells). Tfh cells interact with and activate B cells, which differentiate into plasma cells (which produce high-affinity antibodies to specific viral antigens) or memory B cells. Viral antigens processed in phagolysosomes of infected epithelial cells are presented on the cell surface via MHC molecules. Peripherally circulating cytotoxic T lymphocytes recognise antigen-containing MHC class I molecules via their CD8 co-receptors, and interactions between CD8–T-cell co-receptors and MHC class I molecules activate cytotoxic T lymphocytes, leading to the release of proinflammatory cytokines and cytotoxic granules such as granzymes, which trigger apoptosis of the infected host cell. However, SARS-CoV-2 can hinder the adaptive immune response; the accessory protein ORF8 localises in lysosomes and downregulates trafficking of MHC class I molecules to the surface of epithelial cells, thereby reducing cytotoxic-T-lymphocyte-mediated killing of infected cells and downstream immune activation.<sup>60–62</sup> dsRNA=double-stranded RNA. ISGs=interferon-stimulated genes. ORF8=open reading frame 8. PAMPs=pathogen-associated molecular patterns. Tfh=T follicular helper.

estimates. On a functional level, studies have shown delayed neutralising antibody responses to be associated with fatal outcomes and early neutralisation to correlate with faster viral clearance.<sup>65,68</sup> Considerable evidence is now emerging for a role for the humoral response in preventing reinfection.<sup>6–19</sup> In addition to serum neutralising antibodies, emerging evidence suggests that IgA present in mucosal membranes might contribute to early viral neutralisation to an even greater extent than serum IgG,<sup>69</sup> although the relative contributions of these two aspects of humoral immunity in protecting against (re-)infection remain to be thoroughly investigated.

### Mild disease

In patients with milder COVID-19 who do not require hospital admission, the duration of the humoral response seems to be more variable. A longitudinal study of health-care workers with mild disease found that, although there was substantial heterogeneity between individuals in antibody responses, antibodies against the spike S1 domain (which correlated well with viral neutralisation) became undetectable in 31 of 143 (21.7%) patients over 4–5 months.<sup>70</sup> These results are generally concordant with those of a UK study of 2246 individuals with presentation ranging from asymptomatic to mild-to-moderate disease, which showed similar proportions of reversion to seronegativity by 6 months; however, as also shown by others,<sup>70,71</sup> the findings were closely linked to the choice of immunoassay.<sup>63</sup> A longitudinal study of 15 patients recovering from mild disease, done over a shorter time period, found both persistently circulating anti-RBD IgG and the generation of anti-RBD memory B cells (MBCs) capable of producing neutralising antibodies 3 months after estimated viral exposure.<sup>72</sup> In keeping with this finding, a study of more than 30 000 suspected or confirmed cases (95% of whom had mild or moderate symptoms) reported that 90% of individuals who showed seroconversion had detectable neutralising antibodies that were correlated with anti-spike IgG titres. Moreover, these spike-targeting antibodies persisted for up to 5 months after symptom onset,<sup>73</sup> a timeframe supported by a study of 64 patients convalescing after mild-to-moderate disease.<sup>49</sup> Among those with mild disease, there is also evidence for a high proportion of individuals mounting weak primary humoral responses.<sup>74,75</sup> For example, an investigation of 175 patients recovering from mild disease showed that approximately 30% generated very low titres of neutralising antibodies, with 10 patients having titres below the limit of detection.<sup>75</sup> Notably, antibody titres correlated well with age, with higher levels observed in older patients.<sup>75</sup> Overall, the duration of the humoral immune response is less clear for patients with milder symptoms, and although there is substantial variation within and between studies, the data might be consistent with a prolonged response over 5–6 months.

### Asymptomatic disease

In asymptomatic patients, the decline in circulating antibody levels seems to be more pronounced than that in symptomatic patients. A comparison of 37 asymptomatic and 37 symptomatic patients in China identified similar IgG seroprevalence during the acute phase of the disease (81.1% and 83.8%, respectively).<sup>76</sup> However, in the convalescent phase, 8 weeks after symptom onset, 40.0% of asymptomatic patients reverted to IgG seronegativity compared with only 12.9% of symptomatic patients. There was also a trend for declining IgG titres and neutralisation rates across almost all patients, highlighting the short-lived nature of the circulating

humoral response.<sup>76</sup> Similar conclusions were drawn from an analysis of 63 asymptomatic individuals in Wuhan, China, of whom 36.5% did not produce neutralising antibodies; among those who did, circulating levels began to fall after 25 days.<sup>74</sup> An analysis of 254 SARS-CoV-2-positive individuals showed that outpatients with milder or no symptoms had lower anti-RBD antibody titres (IgA, IgM, and IgG) than did individuals with severe disease requiring inpatient care.<sup>51</sup> Similarly, the declines in antibody titres were more rapid in those with milder symptoms. Pseudovirus neutralisation assays showed that viral neutralisation correlated well with anti-RBD IgG titres, with inpatients showing higher neutralisation activity than outpatients.<sup>51</sup> Together, these studies suggest that although the waning of SARS-CoV-2-specific antibody titres is an intrinsic aspect of the disease course, the initial magnitude of response and the speed of decline vary with disease severity. Nonetheless, the declines in antibody titres noted in these studies are arguably consistent with what is known about humoral dynamics following infection with other respiratory viruses, such as SARS-CoV and MERS-CoV.<sup>20,32</sup>

### Memory B cells

Although circulating antibodies provide a simple means of estimating immune protection, they are not the only measure of long-term immunity. Following viral clearance, the antibody-producing plasmablast population contracts, leaving a pool of specialised MBCs,<sup>77</sup> which probably accounts for the fall in circulating antibodies seen across various studies.<sup>57,59</sup> Whereas neutralising antibodies might decline over 5–12 months, MBCs are maintained or increase in frequency,<sup>77–81</sup> undergo extensive clonal expansion,<sup>80</sup> and can generate potent neutralising antibodies against the RBD upon rechallenge.<sup>72,78</sup> Hence, longevity of MBCs capable of producing neutralising antibodies might counteract the pitfalls of a relatively short-lived circulating antibody response.<sup>78</sup>

The production of MBCs might also provide a useful indication of the time from infection to disease resolution. For example, the frequency of MBCs has been found to correlate negatively with symptom duration<sup>82</sup> and to increase following recovery from infection,<sup>83</sup> indicating a potential role in ameliorating disease severity. Although further studies characterising the dynamics of MBCs after infection and vaccination would be beneficial (panel),<sup>41,84,85</sup> such studies require the use of cumbersome assays that might not be feasible in many clinical, or even academic, settings.

Several studies have noted an increase in atypical populations of MBCs (not expressing or downregulating CD21 or CD27, the classic hallmarks of MBCs) in patients with severe disease, which is in line with findings from chronic infections such as malaria and HIV.<sup>83,86</sup> Although the functional significance of these atypical MBCs is not fully understood, their frequency decreases upon recovery and increases in patients who die from COVID-19,



**Panel: Future research: unanswered questions and proposed studies****What is the minimum protective threshold of anti-SARS-CoV-2 serum neutralising antibodies?**

Human challenge studies<sup>41</sup> are needed in which infectious dose can be carefully controlled and neutralising antibody titres longitudinally measured at post-challenge and rechallenge; limitations of this approach include the potential for susceptibility to be elevated under artificial conditions<sup>84</sup>

**Is protective immunity against homologous rechallenge maintained in the absence of a sufficient primary neutralising antibody response?**

Prospective cohort studies should be undertaken in which individuals are followed from a primary to secondary infection, with serology and genomics analyses at each time point; only patients with no previous known exposure to SARS-CoV-2 should be included

**To what extent does strain variation after primary infection influence the likelihood of reinfection?**

Genomic studies are needed to examine the likelihood of reinfection with homologous strains compared with heterologous strains; in-vitro and in-vivo immunological studies that control for differences in strains are also required

**To what extent does immune memory provide lasting protection against reinfection?**

Memory B-cell and T-cell populations should be measured over time in participants with primary infections; rates of reinfection should be compared in groups of patients classified according to measures of immune memory (eg, memory B-cell pseudoviral neutralising capacity at 6 months after infection)

**Why do some secondary infections result in less severe disease, whereas others cause more severe disease relative to primary infections?**

Patient cohorts should be followed over time, with measures of multiple aspects of the immune response, in addition to clinical characteristics, after primary and secondary exposure; limitations of this type of study might include difficulty in controlling for genetic differences in infecting strains, which could influence the exposure and outcome variables

**How do compartment-specific immune repertoires relate to peripheral blood immune responses?**

Further studies are needed to compare bronchoalveolar lavage fluid with paired samples of blood from infected patients<sup>85</sup>

suggesting an association with poorer patient outcomes.<sup>83</sup> Overall, these findings indicate that clonally expanded pools of MBCs are likely to persist for more than 6 months after primary infection. Although the relative contribution of immune memory towards lasting protection against reinfection with SARS-CoV-2 is unclear (panel), emerging evidence suggests that MBCs might evolve towards non-neutralising profiles over time, particularly in older patients, highlighting the benefit of vaccination.<sup>87</sup>

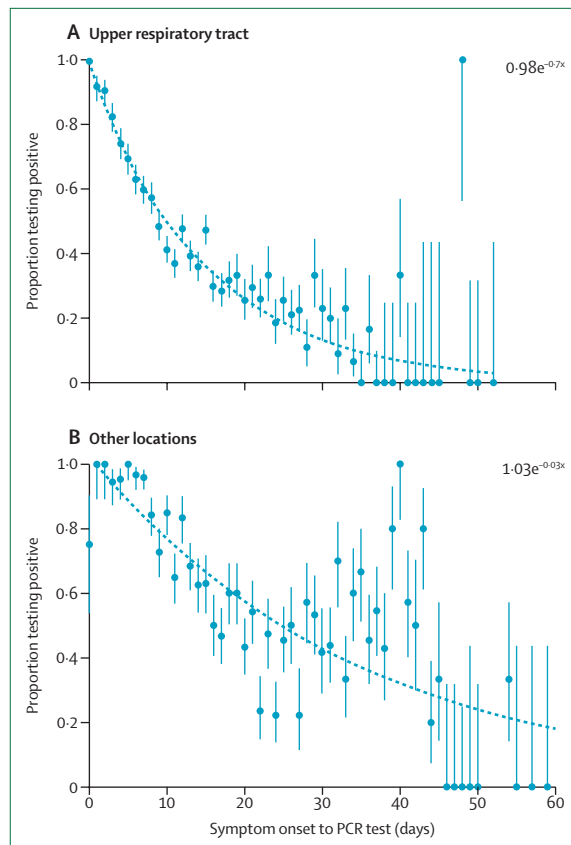
**Cell-mediated immunity in natural SARS-CoV-2 infection**

There is a substantial body of evidence on the role of cellular immunity in response to respiratory virus infection. Whereas antibody responses to a range of respiratory viruses, including SARS-CoV and influenza A virus, are transient, the T-cell response, which is targeted against internal (in the case of cytotoxic T cells) and conserved proteins, tends to be longer lived.<sup>88</sup> For example, in a 6-year follow-up of patients infected with SARS-CoV, memory T cells (MTCs) were found in 61% of patients, whereas MBCs were absent.<sup>27</sup> Various studies of SARS-CoV and MERS-CoV also show the importance of a T-cell response in maintaining long-term immune protection and diminishing the severity of clinical disease.<sup>88–90</sup> Similarly, the severity of COVID-19 is negatively associated with T-cell counts (with lymphopenia being a classic sign of severe COVID-19)<sup>91</sup> and positively associated with the abundance of proinflammatory cytokines.<sup>92–94</sup> Hence, several studies point to the considerable importance of an appropriately

proportioned cell-mediated response in effecting SARS-CoV-2 clearance. The primary focus of these studies, which have encompassed patient cohorts of various clinical severities from several countries worldwide, has been the functional analysis of T cells circulating in the peripheral blood, including key repertoires of CD4<sup>+</sup> helper T cells<sup>95</sup> and CD8<sup>+</sup> cytotoxic T cells<sup>96</sup> (figure 2). However, correlation between peripheral cellular responses and tissue-resident responses can be poor,<sup>85,97</sup> suggesting that future studies should focus on compartment-specific immune repertoires (panel).

**Cell-mediated responses to disease severity**

Various techniques have been used to define epitope specificities of the T-cell response, as its breadth has important implications for the likelihood of viral immune escape. In particular, megapools combining a large number of epitopes have been used to comprehensively map epitope binding specificities of CD4<sup>+</sup> and CD8<sup>+</sup> T cells across the entirety of the viral proteome in patients convalescing from a variety of disease courses, revealing several key insights. First, highly expressed viral proteins tend to have a proportionally large CD4<sup>+</sup> T-cell response mounted against them, with the top three targets including spike (27%), membrane (21%), and nucleocapsid (11%) proteins,<sup>98</sup> an association that is corroborated by other research into CD4<sup>+</sup> and CD8<sup>+</sup> epitope specificities.<sup>99</sup> Second, spike-specific CD4<sup>+</sup> responses correlate well with the magnitude of anti-RBD IgG titres, indicating a coordinated cellular and humoral response to the virus,<sup>98</sup>



**Figure 3: Associations between PCR test positivity and number of days since symptom onset for swabs taken in the upper respiratory tract and other locations**

The raw data, with uncertainties (the narrowest 68% interval in the beta distribution implied by the number of positives and number of negatives on a particular day), are plotted and an exponential fit is shown. The data show that it is possible to test positive more than 6 weeks after symptom onset, especially when the specimen is taken from locations other than the upper respiratory tract (eg, blood or faeces). Data were extracted from a published systematic review of individual data.<sup>113</sup>

indeed, a lack of coordination is associated with more severe disease.<sup>100,101</sup> Third, asymptomatic individuals can develop a robust MTC response even in the absence of detectable antibodies.<sup>98,101–103</sup> Finally, CD4<sup>+</sup> and CD8<sup>+</sup> T cells have a large breadth of epitope binding targets—at 19 and 17 per donor, respectively, in one study.<sup>99</sup> Taken together, these results suggest that cell-mediated immunity to SARS-CoV-2 infection is robust and durable to small mutational changes.

Similar to the humoral response, the magnitude of the cell-mediated response appears to be associated with disease severity. For example, in a two-centre retrospective study of 1018 patients admitted to hospital with confirmed COVID-19, all T-cell counts were lower in non-survivors compared with survivors, a difference that was particularly pronounced for CD8<sup>+</sup> T cells. Indeed, a multivariable analysis adjusting for age, sex, and underlying conditions found that low abundance of CD8<sup>+</sup> T cells was an independent risk factor for mortality.<sup>104</sup> These results

agree with those from a longitudinal analysis of a small cohort of patients with severe disease, which revealed associations between the early detection of IFN- $\gamma$ -secreting T cells specific to SARS-CoV-2, faster viral clearance, and milder symptomatology.<sup>105</sup> In a retrospective study of 522 patients admitted to hospital with COVID-19, total T-cell counts were 60% lower in patients in intensive care than in those with milder disease.<sup>106</sup> There are also negative effects of excessive proinflammatory cytokine production on both patient outcomes<sup>104</sup> and T-cell counts,<sup>106</sup> indicative of a role for overproduction of proinflammatory cytokines in downregulating T-cell survival or proliferation. In keeping with the importance of T cells in mitigating severe outcomes, SARS-CoV-2-specific T-cell counts decrease with increasing age,<sup>106</sup> perhaps accounting for the well documented increased likelihood of poorer prognoses among older individuals.<sup>107</sup> Indeed, in patients with more severe disease, there is upregulation of a marker of T-cell exhaustion, programmed cell death 1 receptor.<sup>106</sup> Taken together, these findings suggest that an effective T-cell response protects against severe outcomes in SARS-CoV-2 infection.

### Cell-mediated aspects of immune memory

The development of cell-mediated immune memory might provide long-term protection against severe disease upon viral rechallenge. Various studies of previous pandemic coronaviruses have shown that MTC responses outlast those of MBCs<sup>27,108</sup> and are protective against severe disease upon rechallenge.<sup>88–90</sup> For example, mice with CD8<sup>+</sup> MTCs, but without CD4<sup>+</sup> MTCs or MBCs, given a high dose of SARS-CoV mounted an effective immune response, including the production of cytokines and cytolytic molecules, which led to reduced viral load and allowed the mice to survive an otherwise lethal dose of SARS-CoV.<sup>90</sup> Research on cell-mediated aspects of SARS-CoV-2 infection has shown that infection leads to the production of long-lived cytotoxic MTCs, with a longitudinal study estimating the half-life of CD8<sup>+</sup> MTCs to be 125–225 days.<sup>81</sup> Moreover, the majority of the CD8<sup>+</sup> MTCs were phenotypically characterised as being terminally differentiated effector memory cells.<sup>81</sup> These MTC subpopulations are protective against severe disease upon influenza A virus challenge,<sup>109</sup> suggesting that secondary infections with SARS-CoV-2 might be milder (however, confounding factors that future studies of this kind might face are outlined in the panel).

Cell-mediated immune memory is important not only in its own right, but also because its coordination with the humoral immune response has a major role in the production of MBCs. T follicular helper (Tfh) cells, a specialised subset of CD4<sup>+</sup> T cells found in the B-cell zone of secondary lymphoid organs, play a key part in this process. These cells provide co-stimulation to germinal centre B cells to effect their positive selection, proliferation, and differentiation into long-lived antibody-secreting plasma cells and MBCs (figure 2).<sup>110</sup> Thus, the analysis of

Tfh cells circulating in the peripheral blood provides a useful proxy to understand the extent of humoral immune memory resulting from SARS-CoV-2 infection.<sup>111</sup> These studies have shown considerable stability in the relative frequencies of memory Tfh cells, including spike-specific cells, over long time periods (>6 months).<sup>81</sup> Notably, Tfh cells expressing chemokine receptor 6, which is associated with reduced COVID-19 severity,<sup>100</sup> comprise a large portion of Tfh cell populations<sup>72,81,100,111</sup> and persist, or even increase,<sup>81</sup> in frequency over relatively long time periods. As T cells are known to target more conserved epitopes than do antibodies,<sup>88</sup> and to have key roles in viral clearance, reduced disease severity upon rechallenge, and the establishment of pools of both affinity-matured B cells and MBCs,<sup>112</sup> these data raise the possibility that cell-mediated immune memory to SARS-CoV-2 could provide effective protection against reinfection; however, questions still remain (panel).

### Humoral immunity and prevention of reinfection

While many studies have examined the temporal dynamics of the humoral response to SARS-CoV-2, a smaller, but growing, number have instead assessed whether a decline in humoral immunity reduces protection from reinfection, a question with implications for the effectiveness of control strategies. Unfortunately, reports of reinfection are confounded by several factors,

including long-lasting positivity to RT-PCR assays (figure 3),<sup>113</sup> persistent viral shedding, and viral reactivation, all of which can introduce uncertainty in distinguishing true cases of reinfection from cases of singular infection with prolonged positivity. Some case studies have been able to disentangle these two distinct possibilities using genomic sequencing, either alone or in combination with information on the period of time between positive tests, sandwiched by one or more negative tests (table 1).<sup>6–14</sup> Cases for which the time periods between primary and secondary infections were short and genetic change minimal, particularly for some patients from China (table 1),<sup>14</sup> might not represent true cases of reinfection but prolonged PCR positivity (patients might remain PCR-positive >6 weeks after infection, especially when the sample is taken from the lower respiratory tract, blood, or faeces;<sup>113,114</sup> figure 3). This risk can be avoided by defining reinfection on the basis of a minimum time interval between primary and secondary infections that is longer than the maximum known duration of PCR positivity (eg, 60 days<sup>16</sup> or 90 days<sup>17,19</sup>), or by using a shorter time period in combination with genomic confirmation.<sup>18</sup> Nonetheless, the remaining cases that are more likely to represent true reinfections suggest that, as the severity of illness upon reinfection appears to be unpredictable, a pertinent area for further research might be the investigation of possible causes of varying symptom severity upon reinfection (panel).

	Age (years)	Sex	Interval between episodes (days)	Disease severity (Ct)		Serology result	
				First episode	Second episode	First episode	Second episode
USA <sup>6</sup>	25	Male	48	Mild (35)	Hospitalised (35)	NA	IgM <sup>+</sup> , IgG <sup>+</sup>
Hong Kong <sup>7</sup>	33	Male	142	Mild (NA)	Asymptomatic (27)	IgG <sup>+</sup>	IgG <sup>+</sup>
Belgium <sup>8</sup>	51	Female	93	Mild (26–27)	Milder (33)	NA	IgG <sup>+</sup>
India <sup>9</sup>	25	Male	108	Asymptomatic (36)	Asymptomatic (17)	NA	NA
India <sup>9</sup>	28	Female	111	Asymptomatic (28)	Asymptomatic (17)	NA	NA
Ecuador <sup>11</sup>	46	Male	63	Mild (37)	More severe (NA)	IgM <sup>+</sup> , IgG <sup>+</sup>	NA
England <sup>*12</sup>	49	Female	38	Moderate (NA)	Severe (NA)	NA	IgG <sup>+</sup>
England <sup>*12</sup>	93	Male	55	Mild (NA)	Moderate (NA)	NA	IgG <sup>+</sup>
England <sup>*12</sup>	82	Male	87	Severe (NA)	Moderate (NA)	IgG <sup>+</sup>	IgG <sup>+</sup>
England <sup>*12</sup>	86	Female	57	Severe (NA)	Asymptomatic (NA)	NA	IgG <sup>+</sup>
England <sup>*12</sup>	62	Female	84	Moderate (NA)	Asymptomatic (NA)	IgG <sup>+</sup>	IgG <sup>+</sup>
England <sup>*12</sup>	83	Male	43	Severe (NA)	Asymptomatic (NA)	NA	IgG <sup>+</sup>
UK <sup>13</sup>	78	Male	256	Mild (26–27)	Critical (28)	IgM <sup>+</sup> , IgG <sup>+</sup>	NA
China <sup>14</sup>	84	Female	33	Critical (33)	Moderate (28)	NA†	NA†
China <sup>14</sup>	33	Male	19	Moderate (32)	Critical (28)	NA†	NA†
China <sup>14</sup>	59	Male	57	Moderate (29)	Moderate (25)	NA†	NA†
China <sup>14</sup>	33	Male	35	Moderate (29)	Asymptomatic (32)	NA†	NA†
China <sup>14</sup>	2	Female	22	Moderate (33)	Asymptomatic (37)	NA†	NA†
China <sup>14</sup>	74	Male	24	Critical (33)	Asymptomatic (24)	NA†	NA†

Data were obtained on Feb 9, 2021. All cases had RT-PCR-negative results between first and second episodes. Ct=cycle threshold. NA=not available. \*Indicates potential reinfection cases that were not confirmed through genomic analysis. †Serological data were not analysed using a cutoff threshold to designate seropositive and seronegative; see original paper for findings.

**Table 1: Early studies of potential SARS-CoV-2 reinfections**



In addition to evidence from case studies, findings from large epidemiological studies provide informative data on the protective effect of the antibody response and risk of reinfection. For example, two large prospective cohort studies from the UK, one that followed 12 541 health-care workers over 7 months<sup>16</sup> and another that followed 20 787 health-care workers over 5 months,<sup>15</sup> estimated that individuals who were seropositive for anti-spike IgG at baseline had an 88% and 83% reduced risk of infection, respectively, relative to those who were seronegative at baseline. In both studies, the median time to reinfection was 5–6 months.<sup>15,16</sup> General population data are currently sparse, but one large digital observational study using a Danish population-level dataset of 4 million individuals<sup>19</sup> adds to the UK studies' findings. Serostatus data were not available, but the 12-month study showed that PCR positivity at baseline was associated with a 77–83% lower risk of reinfection compared with PCR negativity at baseline. However, individuals aged 65 years and older who were PCR-positive at baseline had a 47% reduced chance of reinfection,<sup>19</sup> suggesting that longevity of the sterilising immune response might be reduced in older individuals. The study also showed that the estimated protection against reinfection did not differ by the time since primary infection,<sup>19</sup> suggesting that protection against reinfection might, in fact, last for 12 or more months. The discrepancy between the time-to-reinfection findings of the UK and Danish studies could potentially be explained by the choice of study setting. As health-care workers tend to be in closer proximity to infectious patients and hence are likely to receive higher viral loads, and encounter a greater variety of viral strains, than individuals in the general population, reinfection timeframes might be expected to be shorter in this subpopulation.

Another retrospective cohort study, involving 3.2 million people in the USA, showed that individuals who were seropositive for IgG, IgA, or IgM antibodies at baseline had a ten-times reduced risk of testing PCR-positive 90 days later compared with those who were seronegative at baseline.<sup>17</sup> Corroborating these findings, the results of a prospective cohort study in Qatar indicated that, over a 7-month period, the incidence of reinfection

among initially seropositive individuals was almost 95% lower than that in initially seronegative individuals. Similar to the Danish cohort, there was no evidence of waning immunity against reinfection over the 7-month period.<sup>18</sup> Although observational studies are limited by the short time period since SARS-CoV-2 emergence, current evidence suggests that reinfection can occur within 5–12 months of primary infection, a timeframe that is similar to that for other acute respiratory viral infections (table 2).<sup>15–19,35–37,39,115–122</sup> Nonetheless, it is unclear whether the time to reinfection suggested by the available data could become shorter with escape from neutralisation by variants of concern (VOCs), including (but not limited to) the alpha (B.1.1.7), beta (B.1.351), and gamma (P.1) variants, and the B.1.617 lineage, a subtype of which is the delta variant (B.1.617.2).<sup>123–128</sup> While studies of other respiratory viruses such as human coronavirus and influenza A suggest that homologous reinfection is uncommon,<sup>84,115</sup> the picture is less clear for SARS-CoV-2. Further studies that could be done to investigate this, and related questions, are documented in the panel. Overall, the research highlighted here demonstrates that the humoral response is a key element of the host response to SARS-CoV-2 protection against reinfection.

## Adaptive immunity after SARS-CoV-2 vaccination

### Evidence from vaccine trials

Aside from natural infections, there is also evidence for a robust and potentially long-lasting immune response arising from licensed SARS-CoV-2 vaccines.<sup>4,129</sup> A large variety of SARS-CoV-2 vaccines has been developed, with 11 demonstrating efficacy in phase 3 trials and more than 270 in development.<sup>130,131</sup> Adenoviral vector vaccines in particular, such as those developed for Ebola<sup>132</sup> and malaria<sup>133</sup> and, most recently, SARS-CoV-2,<sup>4,129</sup> are known to induce a robust cellular immune response. For example, a phase 1/2 trial of the SARS-CoV-2 adenovirus vector vaccine ChAdOx1 nCoV-19 (Oxford–AstraZeneca) showed that vaccination elicited a spike-specific T-cell response as early as 7 days after vaccination, which was maintained until day 56.<sup>129</sup> A follow-up phase 2/3 trial using an ex-vivo IFN- $\gamma$  enzyme-linked immunospot

	Influenza A virus	SARS-CoV-2	Respiratory syncytial virus	Human coronavirus
Attachment factor	Haemagglutinin	Receptor-binding domain (spike)	Glycoprotein	Spike
Host receptor(s)	Sialic acid	ACE2, TMPRSS2	CX3CR1, HSPG	APN, ACE2
Case fatality rate	0.5% <sup>116</sup>	~0.2–2.7% <sup>117</sup>	0.3–2.1% <sup>118</sup>	NA <sup>119</sup>
Time to reinfection	6 months–lifelong <sup>*35,120–122</sup>	5–12 months <sup>15–19</sup>	2–24 months	6–105 months <sup>37,115</sup>
Rate of reinfection	1.44–11.99 per 10 000 days at risk <sup>120</sup>	0.13–1.09 per 10 000 days at risk <sup>16</sup>	0.22–12.81 per 10 000 days at risk <sup>39</sup>	0.09–1.10 per 10 000 days at risk <sup>36,115</sup>

Data were extracted from published studies and rates of reinfection were transformed such that they were comparable between studies. ACE2=angiotensin-converting enzyme 2. APN=human aminopeptidase N. CX3CR1=CX3C chemokine receptor 1. HSPG=heparan sulfate proteoglycan. NA=not applicable. TMPRSS2=transmembrane protease serine 2. \*There is some uncertainty as to whether immunity against influenza A is lifelong in some circumstances.

**Table 2: Comparison of basic biological, epidemiological, and immunological features of common respiratory viruses and SARS-CoV-2**

assay on peripheral blood mononuclear cells showed that spike-specific T cells peaked at 14 days after the initial dose and were maintained at high levels across all age groups until the last day of measurement on day 42.<sup>134</sup> Other SARS-CoV-2 vaccines have also shown promise. Early clinical trial data on the mRNA vaccine BNT162b2 (Pfizer–BioNTech) demonstrated 95% effectiveness against disease, measured at least 7 days after the second dose, in people aged over 16 years;<sup>3</sup> however, subsequent data have shown reductions in effectiveness against more recently circulating variants.<sup>125,135</sup> In a phase 1/2 trial of this vaccine, strong and correlated CD4<sup>+</sup> and CD8<sup>+</sup> T-cell responses were raised against a variety of spike epitopes 7 days after the second (booster) dose.<sup>136</sup> Furthermore, the mRNA vaccine mRNA-1273 (Moderna) elicited a robust CD4<sup>+</sup> type 1 helper T-cell response in a phase 1 trial, with concurrent production of IL-2, tumour necrosis factor, and IFN- $\gamma$ .<sup>137</sup> Although vaccine rollout plans involve dosing with homologous vaccine types, results from an in-vivo study suggest that dosing with heterologous types could lead to a more robust cell-mediated response,<sup>138</sup> and hence might provide longer-lasting protection against severe symptoms.

Numerous trials have shown robust humoral responses in participants after vaccination. For example, an increase in anti-spike IgG was observed after administration of the second dose of the ChAdOx1 nCoV-19 vaccine, which correlated well with neutralising antibody titres in all age groups (but see our discussion of vaccine-elicited neutralisation of VOCs, below).<sup>134</sup> In addition, a phase 1/2 trial of the BNT162b2 vaccine identified that neutralising titres following the primary dose exceeded those observed among naturally infected convalescing patients; however, more recent research has found that those infected before vaccination mount similar, or stronger, immune responses than do previously unexposed, double-dose vaccinated individuals.<sup>136,139</sup> In pseudovirus neutralisation assays, serum samples from vaccinated individuals neutralised a diverse range of SARS-CoV-2 spike variants (but see our discussion on immune responses against VOCs).<sup>136</sup> Humoral responses after mRNA-1273 vaccination were also substantial, with serum neutralisation detectable in all participants following the second dose.<sup>137</sup>

### Correlates of protection

Phase 3 vaccine trials, alongside emerging data on reduced cases, hospital admissions, and deaths,<sup>140,141</sup> demonstrate the success of vaccine rollout in various countries worldwide. These trials—undertaken before VOCs were detected—used the neutralising antibody titre as a correlate of protection (ie, an immune marker, or threshold, associated with protection against infection or disease).<sup>139</sup> However, there are several important reasons that appropriate, more specific correlates of protection are still needed, including the identification of key titre thresholds. First, in the absence of reliable correlates of protection, next-generation vaccine development is

likely to lag substantially behind the emergence of novel variants, as large and costly field trials must be undertaken to establish vaccine effectiveness against these newer variants. In the face of vaccine-escape mutants, these randomised controlled trials might become unethical (or, in low-incidence populations, unfeasible). Second, identifying specific correlates of protection would enable direct comparisons of different vaccines through immunological thresholds, rather than via crude effectiveness rates.<sup>130,142</sup> Finally, although not exhaustively, information on correlates of protection could be used to inform mathematical model parameters, with potential uses in predicting the durability of vaccine-derived protection and informing pandemic and post-pandemic interventions.

For acute infections such as SARS-CoV-2, neutralising—or non-neutralising but functional—antibodies are often considered an appropriate correlate of protection,<sup>35,131,143</sup> a supposition supported by the evidence on protection from reinfection.<sup>6–19</sup> Nonetheless, delineating specific titre thresholds is challenging for several reasons—eg, correlates of protection probably differ between infection and vaccination, and between different vaccine types, and might be altered by prior exposure,<sup>136,139,144,145</sup> emerging variants, and immunodeficiency.<sup>143</sup> In addition, whether there is a focus on correlates of protection against infection or disease will probably shape the markers and thresholds that are identified as important; a notable example is measles vaccination, for which specific antibody titres provide protection against disease but not always infection.<sup>143,146</sup> Although SARS-CoV-2 vaccine correlates of protection remain ill-defined,<sup>143,147</sup> a statistical analysis of phase 3 data from seven vaccines indicated that neutralising antibody or IgG titres measured 1–4 weeks after the second dose (both calibrated to a common standard) might explain 78% and 94%, respectively, of the variation in vaccine efficacy.<sup>130</sup> Importantly, these findings are consistent with the reported associations between reduced viral neutralisation of VOCs and reduced vaccine effectiveness,<sup>128,148–151</sup> while possibly also supporting the previously posited notion that vaccine-elicited antibodies need not be neutralising to have a protective effect.<sup>131</sup> Another study that examined immune correlates of protection by incorporating data from seven vaccine trials and from convalescent serum samples into a predictive model estimated the neutralisation titres required for protection against severe disease to be more than 6·5-times lower than those against detectable infection,<sup>152</sup> suggesting that although reinfections might be likely with waning protective immunity, such cases should generally be milder. This model also suggested that neutralising antibody half-lives were similar between natural infection and vaccination.<sup>152</sup> However, further research is required to corroborate these findings, and other immunological markers are likely to have an important influence on protective immunity after vaccination (eg, MBCs),<sup>153</sup> and might explain findings of protection in the presence of low

neutralising antibody titres.<sup>131</sup> A more detailed delineation of correlates of protection, including protective antibody titre thresholds,<sup>152</sup> in addition to other important immunological markers, will be needed to assist epidemiological studies and the development and rollout of next-generation vaccines in the coming months and years.

### Conventional prime-boost strategy

The majority of licensed COVID-19 vaccines use a (homologous) two-dose prime-boost strategy, with only a few exceptions, including the single-dose adenovirus-vector Ad26.COVS.2 vaccine (Janssen).<sup>154</sup> Whether this blanket strategy should be applied irrespective of individual infection history has been called into question by emerging data. Accumulating evidence suggests that the post-vaccine immune response in individuals infected before primary vaccination might be similar to, or even more robust than, that in unexposed individuals receiving conventional prime-boost doses.<sup>136,139,144,145</sup>

However, it is important to note that many uncertainties remain that might make differential provision of second doses on the basis of exposure status<sup>144</sup> a risky strategy. For instance, it is unclear whether exposed, prime-dose vaccinated individuals would have similar protection against reinfection with VOCs compared with unexposed individuals receiving conventional prime-boost doses, although *in-vitro* studies suggest that this might be possible.<sup>153</sup> By contrast, emerging data on vaccine protection against VOCs are clear: two doses provide substantially more protection against infection with VOCs than does one dose, irrespective of the vaccine.<sup>125,135</sup> Additionally, the long-term dynamics of relevant immune cells might differ substantially according to which of these two strategies is used; early data<sup>136,139,144,145,153</sup> are only beginning to emerge to enable rigorous evaluation of this question. A more cautious approach, but one that still recognises the importance of the evidence presented, might be to prioritise second doses for previously unexposed individuals,<sup>144</sup> but to still provide second doses to exposed individuals where logistically possible. Such an approach is supported by data showing that breakthrough infections among recipients of a second dose occur less often in previously exposed than in unexposed individuals (3-month cumulative incidence of 0.42% among previously exposed BNT162b2 booster-dose recipients compared with 0.90% among unexposed booster-dose recipients).<sup>155</sup> Despite this, in resource-poor settings with limited vaccine stocks, focusing second doses on those previously unexposed<sup>153</sup> could provide a means of resource allocation that lessens the burden on public health systems.

### Immune response against variants of concern

The emergence of several variants in late 2020 with substitutions in the RBD (notably Lys417Asn, Glu484Lys,

and Asn501Tyr),<sup>156</sup> which increase binding affinity to ACE2,<sup>157</sup> has led to concerns over the efficacy of vaccines in development. Although there are few data (and fewer peer-reviewed data) on the T-cell response to VOCs, those that exist are encouraging. For example, a study of 121 health-care workers who received the BNT162b2 vaccine showed no change in CD4<sup>+</sup> T-cell activation when serum samples were stimulated with alpha and beta variant spike protein pools compared with the wild-type protein.<sup>158</sup> Furthermore, findings of a study that sampled serum from individuals 14 days after receiving their second dose of the BNT162b2 or mRNA-1273 vaccine suggested that MTCs were equally reactive to the ancestral strain and VOCs (alpha, epsilon [B.1.429, also known as CAL20C], and gamma), with the exception of the beta variant, for which CD4<sup>+</sup> and CD8<sup>+</sup> responses were 29% and 33% lower, respectively.<sup>159</sup> Another study found that CD8<sup>+</sup> T-cell responses from convalescent individuals recognised the majority of epitopes of circulating variants, with the exception of one spike mutation (Asp80Ala) from the beta variant.<sup>160</sup> Although the latter two studies are not based on serum samples from vaccinated individuals, these data suggest that T-cell cross-reactivity should provide some level of protection against VOCs. However, as correlates of protection are ill-defined,<sup>143,147</sup> the extent of epitope mutation that would lead to immune escape from this cross-reactivity remains unclear, although emerging evidence suggests that escape from neutralisation by VOCs might be considerable. Taken together, these results suggest that SARS-CoV-2 vaccination elicits a strong cell-mediated response that might be resilient to changes in the viral genome, including those in the RBD. Nonetheless, there is a paucity of evidence on the cell-mediated response to VOCs, thus limiting our understanding.

Data are also emerging on the humoral response to VOCs, with various studies noting reduced viral neutralisation in response to both natural infection and vaccination.<sup>123,124,156,161–164</sup> Most notable are multiple reports of the beta variant evading neutralisation from the serum of vaccinated individuals. For example, among individuals receiving two doses of the BNT162b2 or mRNA-1273 vaccine, one study found neutralising activity against this variant to be 10–12-times lower than that against the wild-type,<sup>156</sup> while another found 19–42-times reductions in neutralisation.<sup>124</sup> Moreover, these effects appear to translate into diminished vaccine efficacy: a South African trial of the ChAdOx1 nCoV-19 vaccine showed a substantial decrease in efficacy against mild-to-moderate COVID-19 (measured  $\geq 14$  days after the second dose) caused by the beta variant (10% efficacy) compared with earlier South African variants (75% efficacy).<sup>148</sup> These results also agree with those of an interim analysis of a trial of the nanoparticle spike protein vaccine NVX-CoV2373 (Novavax; not yet formally published), which showed lower efficacy against the beta variant than against earlier

variants.<sup>149</sup> Among other variants, viral neutralisation from serum samples of individuals who have received two doses of the BNT162b2 or mRNA-1273 vaccines is also decreased against the gamma and zeta (P.2) variants, by 4–7-times and 3–6-times, respectively.<sup>124</sup> A number of other studies using serum from individuals who received the BNT162b2 or mRNA-1273 vaccines have shown either marginally reduced neutralisation against the alpha variant<sup>163,164</sup> or largely unchanged neutralisation profiles against several variants.<sup>124,156,165</sup> However, further evidence suggests that even this marginal change in immune response is associated with a decrease in two-dose vaccine efficacy against symptomatic infection from 81·5% (BetaCoV/Australia/VIC01/2020 strain) to 70·4% (alpha variant) for the ChAdOx1 nCoV-19 vaccine (measured >14 days after the booster dose)<sup>150</sup> and from 95·6% to 85·6% for the NVX-CoV2373 vaccine (measuring timepoint not yet reported).<sup>151</sup> Early data on the B.1.617 lineage, which has two RBD mutations, suggest that it can evade neutralisation by antibodies induced by infection or vaccination with moderate efficiency.<sup>126,127</sup> Efficacy after a single dose of the BNT162b2 or ChAdOx1 nCoV-19 vaccines against symptomatic disease through delta variant infection has been reported to be 33·5%, rising to 87·9% (BNT162b2) or 59·8% (ChAdOx1 nCoV-19) after two doses (measured ≥3 weeks after vaccination).<sup>135</sup> Nonetheless, symptom onset has been poorly recorded in the testing data and is considered largely unreliable. Furthermore, fully sequenced genomic data are scarce; hence, further published data corroborating these findings are required.

Another method of assessing the durability of vaccine-elicited immunity against VOCs is by examining emerging data on breakthrough infections (those occurring in vaccinated individuals). In a cohort of 417 individuals in New York City, USA, two breakthrough infections were identified in individuals who had received their second dose 19 and 36 days previously.<sup>166</sup> Sequencing data indicated that the SARS-CoV-2 variant in each patient had key spike mutations, including a Glu484Lys mutation in one patient, which is recognised to facilitate viral avoidance of antibody neutralisation. Analysis of serum from this patient revealed high levels of neutralising antibodies,<sup>166</sup> further supporting the notion of viral neutralisation escape from (presumably vaccine-elicited) antibodies. Another study, from Israel, which sequenced genomes from 817 nasopharyngeal swabs of BNT162b2-vaccinated individuals showed that the alpha and beta variants were disproportionately represented in breakthrough infections (defined as those occurring ≥14 days after the prime dose, or ≥7 days after the booster dose). Specifically, compared with unvaccinated controls, a higher proportion of booster-dose vaccinated individuals showed evidence of beta-variant infection, whereas a higher proportion of prime-dose vaccinated individuals were infected with the alpha variant.<sup>167</sup> Other reports of similar breakthrough infections with VOCs are also emerging.<sup>155,168</sup>

Of the study designs that allow for prevalence estimation, breakthrough infections have thus far been identified among prime-dose recipients with a prevalence of 2·6% (BNT162b2 or mRNA-1273 vaccinees, no sequencing performed),<sup>169</sup> and among booster-dose recipients with a prevalence of 0·48% (BNT162b2 or mRNA-1273 vaccinees, alpha variant or iota-like variant [B.1.526 lineage]),<sup>166</sup> 0·89% (BNT162b2 vaccinees, all alpha variant),<sup>155</sup> and 2·0% (BNT162b2 or mRNA-1273 vaccinees, no sequencing performed).<sup>169</sup> Another study, which did not group participants by vaccine dose, found a prevalence of breakthrough infections of 1·13% among individuals who received the BNT162b2 or mRNA-1273 vaccines, although no sequencing was performed to identify the variants.<sup>168</sup> Owing to the relatively short time since vaccine rollout began, it remains to be seen whether breakthrough infections will become substantially more frequent in the coming months. These early data nonetheless suggest that the durability of vaccine-induced immunity is affected by VOCs. Encouragingly, however, breakthrough infections appear to infrequently result in onwards transmission, and to occur less often in previously exposed individuals who have been vaccinated.<sup>155</sup>

Overall, data on the immune response to VOCs demonstrate the need for broadly protective SARS-CoV-2 vaccines (as also suggested by several others<sup>6,163</sup>). Although the mutation rate of coronaviruses is notably lower than, for example, that for influenza A virus—and hence, in the majority of vaccinated individuals, protection is unlikely to be lost completely beyond 12 months<sup>170</sup>—in the short-to-medium term current vaccines will require updating to maintain their effectiveness; indeed, this development is already underway for the gamma and beta variants.<sup>148</sup> Precisely when this change will need to occur will be guided by advances in our ability to specifically classify immune correlates of protection.<sup>147</sup> Moreover, it is likely that, even with improved understanding of correlates of protection, vaccine development and deployment will lag substantially behind outbreaks caused by novel VOCs and, therefore, vaccination alone might be inadequate to preclude further epidemics. Particular attention should be paid to higher-risk populations, including immunocompromised patients and those on immunosuppressant drugs, who might not mount durable immune responses, particularly when vaccination is improperly coordinated with immunosuppressant therapy (as demonstrated among immunosuppressed patients receiving pneumococcal and influenza vaccines).<sup>171</sup> Among the general population, the lower prevalence of SARS-CoV-2 brought about by vaccination and non-pharmaceutical interventions should nonetheless lead to a lower rate of novel variant emergence,<sup>172</sup> meanwhile enabling the development of secondary vaccines and other interventions.

As of Oct 1, 2021, some countries have begun to offer third doses of vaccinations to higher-risk individuals, including severely immunocompromised patients,



### Search strategy and selection criteria

We searched PubMed and Google Scholar for articles published in English from database inception until March 29, 2021—and updated the search on May 17, 2021, and July 26, 2021, as the paper was revised—using various combinations of the terms “COVID-19”, “SARS-CoV-2”, “humoral”, “antibody”, “cell-mediated”, “T-cell”, “immunity”, “memory”, “reinfection”, and “variant(s) of concern”. Articles resulting from these searches (approximately 1000–7000 results from our PubMed search on May 17, 2021, depending on search term combinations) and relevant references cited in these articles were reviewed. Studies of robust design with relevance to the main aim of this Personal View—to provide readers with a view of what we have learnt about the longevity of protective immunity—were included. High-quality preprints with findings that pertained to the aims of the paper were considered; final publication details were added, where possible, as the paper was prepared for publication.

older individuals, and health-care workers.<sup>173,174</sup> This approach, which has been the subject of discussion in articles published since our literature search was completed, might be supported by data showing waning immunity against infection with the delta variant since the last vaccination,<sup>175</sup> and by studies suggesting that a third dose increases the magnitude and breadth of viral neutralisation.<sup>176</sup> However, concerns about the equity of such a decision have been raised—in particular, the equity of offering third doses in high-income countries while many low-income and middle-income countries have insufficient vaccine stocks to obtain adequate first-dose and second-dose coverage.<sup>177</sup> The question of whether third doses should be provided to the wider population, rather than to specific subpopulations only, is also under consideration.<sup>173</sup>

### Conclusions and future outlook

In this Personal View, we have evaluated evidence on the adaptive immune response to SARS-CoV-2 infection and vaccination, and discussed the relative contributions of humoral and cell-mediated immunity in providing protection against reinfection. Although the immune correlates of protection are ill-defined, neutralising antibodies and functional T-cell responses are often used to infer the robustness of the immune response to SARS-CoV-2 challenge.

Upon natural infection, the T-cell-mediated response appears to be targeted across a larger variety of epitopes than the humoral response, and hence might be more durable to genetic changes in key immunogenic viral epitopes. Nonetheless, the neutralising antibody response also comprises a key aspect of protection against reinfection. Coordination between the two types of adaptive immune response is likely to be important to

mitigate the most severe consequences of infection. Populations of specific memory B cells and T cells remain stable or even increase in size many months after SARS-CoV-2 exposure, which might reduce the likelihood of severe disease upon reinfection. The available evidence suggests that reinfection could occur within 5–12 months of a primary infection and is more likely in individuals who are seronegative for IgG antibodies. Interventions to inhibit transmission of SARS-CoV-2 might be required even in places where the herd immunity threshold has been reached naturally or artificially, and observed increases in severity and transmissibility will further drive the imperative for localised or national non-pharmaceutical interventions.

Compared with the immune response to natural infection, vaccination elicits a response of greater magnitude and higher specificity, largely focused on the RBD. Increasing evidence of reduced neutralisation and vaccine effectiveness against emerging variants, alongside emerging data on breakthrough infections, suggests that vaccines will need to be updated in the short-to-medium term. Such updates will be greatly aided by further investigation of vaccine immune correlates of protection. Since completing our literature search on July 26, 2021, several key reports have been published that encourage cautious optimism. For instance, a prospective cohort study of the Scottish population (2·57 million people)<sup>178</sup> showed that during the winter of 2020–21 (the peak of the pandemic), among individuals who had received one dose of either BNT162b2 or ChAdOx1 nCoV-19 vaccine, only 1196 were admitted to hospital or died due to SARS-CoV-2 infection (<0·1% of the cohort). These findings agree with those from a large study of US health records,<sup>179</sup> which showed that two-dose vaccine (BNT162b2) effectiveness against hospital admission following infection with the delta variant remains at 93% up to 6 months after second-dose vaccination, despite waning effectiveness against infection (from 88% in the first month after the second dose to 47% after 5 months). New data also show that the odds of having long-lasting symptoms ( $\geq 28$  days post-infection) is halved among those who received their second dose of either BNT162b2, ChAdOx1 nCoV-19, or mRNA-1273 at least 28 days previously, compared with unvaccinated individuals (odds ratio 0·51).<sup>180</sup> Ultimately, the duration of protective immunity from natural infection and from vaccination will determine the frequency of outbreaks (eg, annual, biennial, or more sporadic)<sup>181</sup> and the burden on health-care systems of symptomatic disease, and in turn shape the public health policies of nations around the world in the years to come.

### Contributors

TW and TH conceived the article idea. GM, TW, and TH collated and interpreted the published literature and wrote the first draft of the Personal View, with subsequent input and critical review from CS, NG, AJ, and RMA. All authors contributed substantially to the text and take full accountability for the accuracy and integrity of the work.



# Declaration of interests

GM was, at the time of writing, a research analyst for the Infectious Disease Modelling Team at the Joint Biosecurity Centre (JBC) of the UK Government Department of Health and Social Care. TH was, at the time of writing, a research analyst for National Alerting and Assessment at the JBC. TW leads the Infectious Disease Modelling Team at the JBC. AJ is a senior data scientist at the Department of Health and Social Care. NG is a senior public health consultant for emergency response at Public Health England. The authors declare no competing interests in relation to the content of this Personal View.

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